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Abstract: PURPOSE:: To report on the concentration of lipocalin-like prostaglandin D synthase (L-PGDS) in the aqueous humour (AH) in patients with open-angle glaucoma (OAG). **PATIENTS AND METHODS::** Prospective assessment in 20 patients (13 female, 7 male, mean age 74 ± 10.6 y) who underwent surgery for OAG. AH was sampled and analyzed for L-PGDS concentration. AH from 26 patients (11 female, 15 male, 72.4 ± 14.4 y) without glaucoma who underwent cataract surgery, served as control subjects. **RESULTS::** The L-PGDS concentration in the AH sampled from the anterior chamber in the OAG group (5.9 ± 2.4 mg/L) was significantly ($P < 0.001$) higher than in the control group (3.3 ± 1.3 mg/L). There were no significant differences between the concentrations of L-PGDS between the left and the right eye or between genders. **CONCLUSIONS::** L-PGDS concentration in the AH of patients with OAG was significantly elevated compared with its concentration in the AH of nonglaucomatous eyes. As L-PGDS is a biologically pluripotent protein, its possible role in glaucoma warrants further examination.

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Lipocalin-like Prostaglandin D Synthase (L-PGDS) Concentration in Aqueous Humour in Patients With Open-angle Glaucoma

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Purpose: To report on the concentration of lipocalin-like prostaglandin D synthase (L-PGDS) in the aqueous humour (AH) in patients with open-angle glaucoma (OAG).

Patients and Methods: Prospective assessment in 20 patients (13 female, 7 male, mean age 74 ± 10.6 y) who underwent surgery for OAG. AH was sampled and analyzed for L-PGDS concentration. AH from 26 patients (11 female, 15 male, 72.4 ± 14.4 y) without glaucoma who underwent cataract surgery, served as control subjects.

Results: The L-PGDS concentration in the AH sampled from the anterior chamber in the OAG group (5.9 ± 2.4 mg/L) was significantly ($P < 0.001$) higher than in the control group (3.3 ± 1.3 mg/L). There were no significant differences between the concentrations of L-PGDS between the left and the right eye or between genders.

Conclusions: L-PGDS concentration in the AH of patients with OAG was significantly elevated compared with its concentration in the AH of nonglaucomatous eyes. As L-PGDS is a biologically pluripotent protein, its possible role in glaucoma warrants further examination.

Key Words: lipocalin-like prostaglandin D synthase, β -trace, open-angle glaucoma, aqueous humour

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The pathology of open-angle glaucoma (OAG) is still poorly understood. Elevated intraocular pressure (IOP) is the best established risk factor for the development and progression of OAG,^{1,2} but there remain patients who develop typical glaucomatous field and disc changes despite IOPs consistently in the range generally considered normal. In some of these patients, who are said to have “normal-tension glaucoma” (NTG) or “low-tension glaucoma,”³ vascular dysregulation is thought to be a risk factor for the development of disc cupping and visual field loss.⁴ In others, recent research regarding the pathophysiology of the disorder has focused on the anatomy of the subarachnoid space (SAS) surrounding the orbital portion of the optic

nerve and of the content of the cerebrospinal fluid (CSF) in this space.⁵ In addition the effect of the translaminal pressure gradient on the lamina cribrosa may be important.^{6,7} Additional research in this area has focused on humoral abnormalities in patients with OAG. A number of molecules are currently under investigation, such as endothelin-1,⁸ vascular endothelial growth factor,⁹ tumor necrosis factor- α ,¹⁰ matrix metalloproteinases, and their inhibitors.¹¹

Lipocalin-like prostaglandin D synthase (L-PGDS, also called β -trace protein) is a mainly brain-derived protein with a molecular mass of 28 kD. It is the most abundant protein in CSF.^{12,13} It has been reported to induce neuronal cell protection and neuronal cell loss, depending on the receptor pathway it signals to target cells.^{14–16} In the rat eye, L-PGDS was found in the retinal pigment epithelium and in the interphotoreceptor matrix.^{17,18} In addition, messenger ribonucleic acid for prostaglandin D₂ has been described in the retina.¹⁹ The retinal pigment epithelium is suggested to be the predominant site of production for prostaglandin D₂, which is synthesized by L-PGDS, in the eye.¹⁸ Astrocytes (in vitro) are another source of L-PGDS production.²⁰ Recently it has been shown that L-PGDS inhibits astrocyte proliferation and adenosine triphosphate production in vitro.²¹ L-PGDS has also been shown to be upregulated in the local CSF in patients with papilledema from a variety of causes.²² In addition, a study of patients with NTG demonstrated a L-PGDS concentration gradient between the CSF obtained from the SAS surrounding the optic nerve during optic nerve sheath fenestration and the lumbar CSF obtained by lumbar puncture.²³

L-PGDS is a pluripotent protein in the central nervous system and in some structures of the eyeball. In order to evaluate its potential role in OAG we measured its concentration in the anterior chamber of glaucomatous eyes and in eyes without glaucoma. To the best of our knowledge this is the first quantitative analysis of L-PGDS concentration in the aqueous humour (AH) of human OAG patients.

PATIENTS AND METHODS

Twenty patients (overall mean age, 73.8 ± 10.6 y)—13 women (mean age, 78.0 ± 7.7 y) and 7 men (mean age, 65.9 ± 11.2 y)—with a diagnosis of OAG based on optic disc appearance and visual field defects were recruited for a prospective study. Twenty-six patients (mean age, 72.4 ± 14.4 y)—11 women (mean age, 77.3 ± 9.2 y) and 15 men (mean age, 68.7 ± 16.6 y)—with normal appearance of their optic discs and without pseudoexfoliation (PEX) or obvious anterior chamber angle abnormalities and without

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known visual field defects undergoing cataract surgery, were enrolled prospectively and served as controls. All patients and controls underwent complete ophthalmological examination. None of the OAG patients had undergone previous trabeculectomy and none had undergone cataract surgery within the last 6 months.

All of the OAG patients had been treated with IOP-lowering topical medication for at least several weeks at the time of surgery and sampling of AH, and 3 also had been taking acetazolamide for several weeks. Sixteen of the 20 patients (80%) underwent trabeculectomy because of insufficient IOP lowering or adverse effects of the topical and/or systemic treatment. Of these 16 patients, 12 (mean age, 72.8 ± 10.5 y) underwent trabeculectomy only, whereas 4 (69.8 ± 10.8 y) underwent combined trabeculectomy and cataract surgery. The remaining 4 OAG patients (80.8 ± 9.9 y) had IOPs that were deemed to be in the appropriate range, were tolerating their topical medication well, and underwent only cataract surgery. Mean IOP in the OAG patients was 22.0 ± 6.0 mm Hg, ranging from 13 to 34 mm Hg (median, 21.5 mm Hg). Mean IOP in the control group was 14.4 ± 3.1 mm Hg, ranging from 10 to 19 mm Hg (median, 14.5 mm Hg) (Table 1).

AH (0.1 to 0.2 mL) was sampled from the anterior chamber at the beginning of the operation using a 26-G needle (Terumo, Belgium) and a sterile syringe (Omnifix U-100 Insulin, Braun, Germany). Special care was taken not to apply fluids before sampling AH so as not to induce diluting effects. L-PGDS concentration was measured using a fully automated, standard BNII nephelometer (Dade Behring, Marburg, Germany) and commercial reagents. Before determination of L-PGDS, 7-point calibration curves were generated. If necessary, samples were diluted so that the results would fall in the linear range. Daily controls with appropriate standards are obtained to guarantee stability of the system. The minimal quantity of fluid required for reliable nephelometry is 0.02 mL. At least 3 measurements were performed from each sample and mean value was calculated. Three different surgeons from the same department were involved; all measurements were made in the same laboratory.

Statistical analyses were conducted with SPSS statistical analysis software (SPSS Inc., Chicago, IL). An independent 2-tailed *t* test and the Spearman nonparametric correlation coefficient ρ were used, unequal variances were assumed.

This study was designed and performed according to the tenets of the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was provided by all patients and control subjects.

RESULTS

The subjects in the OAG and control groups did not differ significantly in age for women ($P = 0.84$) or men ($P = 0.64$). In the 20 OAG patients, the mean concentration of L-PGDS in the AH was 5.9 ± 2.4 mg/L, with no difference between right and left eyes [$P = 0.79$; right eyes ($n = 12$): 5.8 ± 2.8 mg/L; left eyes ($n = 8$): 6.1 ± 1.7 mg/L], or between women and men [$P = 0.48$; women ($n = 13$): 5.7 ± 2.7 mg/L; men ($n = 7$): 6.4 ± 1.8 mg/L]. In the 12 OAG patients who underwent trabeculectomy, mean L-PGDS concentration in the AH was 6.2 ± 2.6 mg/L, whereas in the 4 patients who underwent combined trabeculectomy and cataract surgery, mean L-PGDS was

5.8 ± 2.9 mg/L. In the 4 OAG patients who underwent only cataract surgery, mean L-PGDS concentration in the AH was 5.4 ± 1.8 mg/L. In the 26 control subjects, the mean concentration of L-PGDS in AH was 3.3 ± 1.3 mg/L. As in the case of the OAG patients, there was no difference in L-PGDS concentration between right and left eyes [$P = 0.87$; right eyes ($n = 16$): 3.3 ± 1.5 mg/L; left eyes ($n = 10$): 3.2 ± 1.0 mg/L] or between women and men [$P = 0.93$; women ($n = 11$): 3.3 ± 1.5 mg/L; men ($n = 15$): 3.3 ± 1.2 mg/L]; however, the mean L-PGDS concentration in the AH obtained from the OAG patients was significantly higher than the concentration from the controls ($P < 0.001$; Fig. 1).

In the OAG group, there were no significant differences in concentration of L-PGDS in AH among patients who underwent trabeculectomy, combined trabeculectomy, and cataract surgery, or just cataract surgery ($P > 0.53$), nor were there significant differences between the OAG patients with PEX and without PEX ($P = 0.13$; mean for OAG with PEX = 7.1 ± 3.1 mg/L; mean for OAG without PEX = 5.1 ± 1.5 mg/L). Mean L-PGDS concentration in the AH from 16 OAG patients treated with topical prostaglandin analogs was 5.8 ± 2.0 mg/L, which was not significantly ($P = 0.75$) different from the 4 OAG patients who were not being treated with topical prostaglandin analog therapy (6.5 ± 4.1 mg/L).

Mean IOP in the OAG group (22.0 ± 6.0 mm Hg) was significantly ($P = 0.003$) higher than in the control group (14.4 ± 3.1 mm Hg). The IOP differences between women and men were not significant in the OAG group ($P = 0.40$) or in the control group ($P = 0.64$), nor were there significant differences in IOP between right and left eyes in either the OAG group ($P = 0.75$) or the control group ($P = 0.81$). The preoperative IOP in the 4 OAG patients who underwent cataract surgery was significantly lower than the preoperative IOP in the 12 OAG patients who underwent trabeculectomy ($P = 0.002$) but did not differ significantly from that of the 4 OAG patients who underwent combined trabeculectomy and cataract surgery ($P = 0.16$). There was no significant difference ($P = 0.99$) in IOP between the 16 OAG patients who were being treated with prostaglandin analogs and the 4 OAG patients who were not being treated with any of these drugs. There was also no significant difference in preoperative IOP between OAG patients with and without PEX ($P = 0.29$; mean for OAG with PEX = 23.8 ± 6.3 mm Hg; mean for OAG without PEX = 20.8 ± 5.8 mm Hg).

There was no significant correlation (Spearman correlation coefficient) between L-PGDS concentration and age ($P = 0.63$, $\rho = 0.074$) or systemic dosage of acetazolamide ($P = 0.098$, $\rho = 0.247$); however, if analyzing all patients and controls together in 1 group, L-PGDS concentration was significantly correlated with preoperative IOP ($P = 0.006$, $\rho = 0.40$), whereas when OAG patients and controls were analyzed separately, there was no significant correlation between L-PGDS concentration and IOP (OAG patients: $P = 0.204$, $\rho = 0.297$; controls: $P = 0.88$, $\rho = 0.031$; Fig. 2).

Subgroup analysis of the 4 OAG patients who underwent cataract surgery only together with the control group did not reveal a significant correlation between L-PGDS concentration and IOP ($P = 0.678$, $\rho = 0.79$). These 4 OAG patients showed a significantly lower IOP than the rest of the OAG group ($P = 0.002$), as did the control group ($P = 0.003$). Comparing only these 4 OAG patients with the control group and assuming unequal

TABLE 1. Values for Preoperative (Pre-OP) Intraocular Pressure (IOP) and for Lipocaline-like Prostaglandin D Synthase (L-PGDS) Concentration in Aqueous Humour (mg/L) of Open-angle Glaucoma Patients and Nonglaucomatous Controls (Co) Undergoing Trabeculectomy (TE), Cataract Surgery (Cat), or Combined Surgery (TECat)

Case Number	Patients and Controls			Aqueous Humour			Pre-OP IOP and Medication					
	OP	Gender	Age	PEX	Side	L-PGDS (mg/L)	IOP (mm Hg)	AAA	PA	BB	α -2A	AAA syst (mg)
Glaucoma-Patients												
1	TE	M	79	X	L	9.9	27	X	X	X		
2	TE	F	78		R	4.0	24	X	X	X		
3	TE	M	58	X	R	7.1	25	X	X	X	X	750
4	TE	F	83		L	4.7	15	X	X	X		
5	TE	M	58		L	5.6	33	X	X	X		750
6	TE	F	77		R	2.5	26	X	X	X	X	
7	TE	M	81	X	L	5.1	21	X	X	X	X	250
8	TE	M	72		L	6.3	13	X	X	X		
9	TE	F	62		L	6.1	24	X	X	X	X	
10	TE	F	82	X	R	6.3	29	X	X	X		
11	TE	F	84	X	R	12.0	34	X	X	X	X	
12	TE	M	59		L	4.4	21	X	X	X		
13	Cat	F	90		R	7.2	18	X	X	X		
14	Cat	F	78		R	3.8	18	X	X	X		
15	Cat	F	68		R	3.9	15	X	X	X		
16	Cat	F	87		L	6.7	17	X	X	X		
17	TECat	F	78	X	R	2.3	16	X	X	X		
18	TECat	F	75	X	R	5.1	22	X	X	X		
19	TECat	F	72	X	R	9.2	16	X	X	X		
20	TECat	M	54		R	6.5	25	X	X	X	X	
Controls												
Co1	Cat	F	59		L	2.9	16					
Co2	Cat	F	85		R	6.3	14					
Co3	Cat	F	84		R	3.7	10					
Co4	Cat	F	85		L	3.4	12					
Co5	Cat	F	83		L	4.2	15					
Co6	Cat	M	85		R	3.3	17					
Co7	Cat	M	78		L	5.4	12					
Co8	Cat	F	65		R	2.6	15					
Co9	Cat	F	69		R	2.3	19					
Co10	Cat	M	70		L	3.0	17					
Co11	Cat	M	76		R	4.1	16					
Co12	Cat	M	71		L	4.1	13					
Co13	Cat	M	79		L	2.7	11					
Co14	Cat	M	82		R	1.9	10					
Co15	Cat	F	73		R	3.3	19					
Co16	Cat	M	65		L	2.9	18					
Co17	Cat	M	25		R	3.9	14					
Co18	Cat	M	43		R	6.0	16					
Co19	Cat	F	83		R	3.6	10					
Co20	Cat	F	84		R	0.2	18					
Co21	Cat	M	61		R	1.7	10					
Co22	Cat	M	80		R	2.8	12					
Co23	Cat	F	80		L	3.3	14					
Co24	Cat	M	57		L	1.8	10					
Co25	Cat	M	80		R	3.2	19					
Co26	Cat	M	79		L	2.7	17					

Reported for pseudoexfoliation (PEX) and IOP lowering medication, for example, acetazolamide (AAA) topical or systemic (syst), prostaglandin analogs (PA), β -blocker (BB), and α -2-agonists (α -2A).
F indicates female; L, left; M, male; R, right.

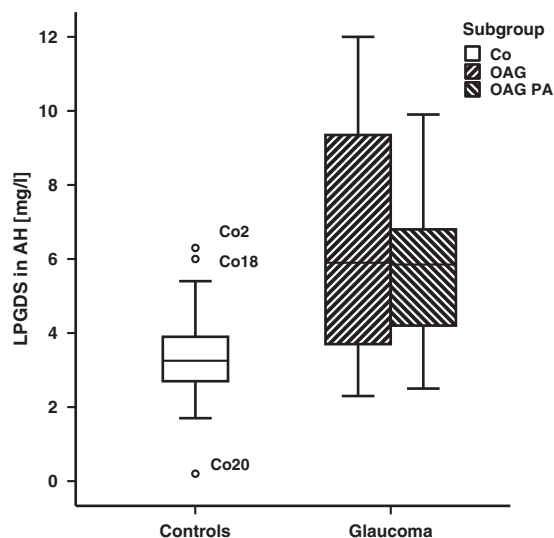


FIGURE 1. Concentration (mg/L) of lipocaline-like prostaglandin D synthase (L-PGDS) in aqueous humour (AH) of open-angle glaucoma patients, separated for patients treated with topical prostaglandin analogous (OAG PA) medication and glaucoma patients without prostaglandin analogous (OAG), and simple cataract patients serving as controls (Co). Box plot indicating median, upper, and lower quartile and SD of values, numbers representing outliers (confidence interval 95%) corresponding with case number in Table 1.

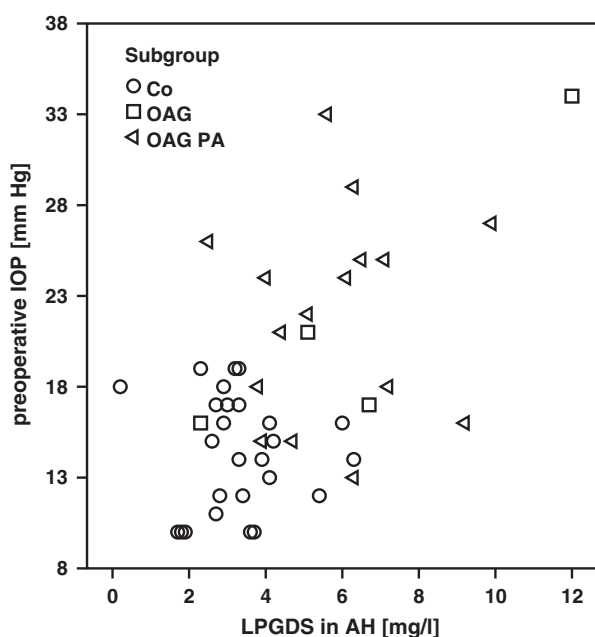


FIGURE 2. Scatter plot of concentration of lipocaline-like prostaglandin D synthase (L-PGDS; mg/L) in the aqueous humour (AH) and preoperatively intraocular pressure (IOP; mm Hg) measured by goldmann applanation tonometry, of open-angle glaucoma patients with prostaglandin analogous topical medication (OAG PA) and without prostaglandin analogous topical medication (OAG), and nonglaucomatous cataract patients serving as controls (Co).

variances, there was no statistically significant difference for L-PGDS concentration ($P = 0.096$), whereas there was a significant difference in IOP (controls mean: 14.4 ± 3.1 mm Hg; 4 purely cataract surgery OAG patients 17.0 ± 1.4 mm Hg; $P = 0.022$). Assuming equal variances and comparing the same 2 subgroups the unpaired 2-tailed t test showed an insignificant difference for IOP ($P = 0.116$) but a significant difference for L-PGDS concentration ($P = 0.007$).

DISCUSSION

In this study of the substance L-PGDS in the AH of patients with OAG compared with control subjects without OAG, we found the concentration of L-PGDS in the AH of the OAG patients (mean 5.9 ± 2.4 mg/L) to be significantly higher than in the controls (3.3 ± 1.3 mg/L). The concentration of L-PGDS in the serum of normal human adults is very low (< 0.55 mg/L),²⁴ whereas reference values for L-PGDS in normal human CSF are at least 30 times higher (15.3 ± 2.7 mg/L).²⁵ The range of L-PGDS concentration in AH found in the OAG and in the control group is between the normal values for serum and CSF. A local L-PGDS production in structures of the eye, has already been demonstrated in mice and rats.¹⁹ Additional proof for local production of L-PGDS in the eye was indicated in a study that investigated the concentration of L-PGDS in the sub-retinal fluid in retinal detachment. The authors of this study found that the L-PGDS concentration correlated with the duration of the detachment,²⁶ being high in patients with a short history of symptoms and low in longstanding detachments.

The present study describes an interesting and significant correlation between the L-PGDS concentrations in the AH and the preoperatively IOP if analyzing all patients and controls at once; specifically, the higher the preoperatively measured IOP, the higher the L-PGDS concentration in the AH. Even if a selection bias could lead to this correlation (because mainly patients with so far insufficient IOP lowering treatment were indicated for interventional therapy of OAG), it seems possible that there is IOP sensitive increase in L-PGDS expression of the intraocular tissue in patients with OAG. However, if subgrouping and analyzing OAG and control patients separately we were not able to find a significant correlation between L-PGDS concentration and IOP. Because of the small number of samples, which is probably the main limitation of this study, further subgroup analysis seem not to yield reliable results, which can be seen in the Results section (ie, analysis of the small subgroup of the 4 OAG patients who underwent only cataract surgery and who had lower IOP values than the rest of the OAG group). Therefore, the question of mechanosensitivity needs to be addressed in a larger cohort of OAG patients and in patients with NTG.

The possible role of L-PGDS in the pathophysiology of glaucoma needs to be addressed and concerning its possible pathophysiological mechanisms. Several mechanisms may be involved. L-PGDS is a prostaglandin synthase with a pluripotent activity. In particular, it has apoptosis-inducing properties in neuronal tissue.^{13,15,16,25} In addition, immunofluorescence studies in nonhuman primate brains has demonstrated a close spatial relationship of L-PGDS to astrocytes and oligodendrocytes.²⁷ These cell types are mainly located in white matter tissue, such as the optic nerve. The hallmark of glaucomatous optic neuropathy is excavation of

the optic disc due to the progressive loss of nerve fibers. In contrast to the normal disc, the lamina cribrosa, which builds the barrier between the SAS and the vitreous cavity, in a patient with glaucoma can possibly lose its tightness as the space that might be left empty by the degenerated nerve fibers could function as a “canal.” Therefore a connection between the SAS and the vitreous cavity could be postulated. Through this route, L-PGDS from the CSF might enter the eyeball and the anterior chamber.

In order to elucidate the relation between elevated L-PGDS levels in AH and IOP, further studies measuring L-PGDS concentrations in AH of patients with NTG and patients with ocular hypertension are needed.

This study does not address the question whether the elevated L-PGDS concentration in the AH of OAG patients is part of the pathomechanism of glaucomatous optic disc changes or is an epiphenomenon, the consequence of the pathological changes in the metabolism of glaucomatous eyes in general; however, in light of the recently reported effect of L-PGDS on astrocytes and their adenosine triphosphate production *in vitro*²¹ and the previously reported effects on other neuronal cells,^{28,29} it seems feasible that L-PGDS concentration could play an important role in modulating apoptosis or survival of neuronal cells in glaucomatous optic neuropathy.

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